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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/673,739	10/20/2000	Thomas Valentine McCarthy	1377-156P	3757

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EXAMINER
TUNG, JOYCE

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 05/21/2003

24

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Application No.	Applicant(s)
09/673,739	McCarthy et al.
Examiner	**Art Unit**
Joyce Tung	1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED *Apr 2, 2003* FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *Aug 29, 2002*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see NOTE below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____

3. ☐ Applicant's reply has overcome the following rejection(s):

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because:
Please see the attached.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____

Claim(s) objected to: _____

Claim(s) rejected: *1-21 and 23*

Claim(s) withdrawn from consideration: _____

8. ☐ The proposed drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____.

10. ☐ Other:

This Office action replies the response filed 4/02/2003.

The amendment after final filed 1/30/2003 has been entered. Following the entry of the amendment, claims 1-21 and 23 are pending.

Response to Applicant's Amendment/Arguments

1. Applicant's arguments with respect to the claimed invention have been fully and carefully considered but they are not persuasive because the response filed 4/2/2003 argues that the examiner's statement in the advisory action mailed 1/14/2003 is unclear and contradictory in which the examiner's first state the teachings of McCarthy et al., instead of citing to particular portion of McCarthy et al. to support the rejection, instead of that examiner cites the teachings of Dianov et al.

The reason to cite the teachings of Dianov et al. is that cleaving phosphate linkage of DNA molecule at an abasic site in which the 3' hydroxyl terminus is generated was well known in the art at the time of the instant invention as taught by Dianov et al. (See pg. 1606, fig. 1 of the reference of Dianov et al.).

Although the response argues that McCarthy et al. do not disclose that cleaving phosphate linkage of DNA molecule at an abasic site in which the 3' hydroxyl terminus is generated, this reaction generating 3' hydroxyl terminus is encompassed in the teachings of Dianov et al. (See pg. 1606, fig. 1 of the reference of Dianov et al.).

The response also argues regarding the issue that the claims do not specify which group of the DNA is cleaved and the teachings of McCarthy et al. encompasses the limitations in the

claims. The examiner agrees that the claims dictate where the cleavage occurs and McCarthy et al. encompasses the limitations in the claims.

The response further argues regarding the reference of Chirikjian et al. that the glycosylase of Chirikjian et al. recognizes and cleaves mismatches, the present invention does not involve mismatch and the glycosylase of the present invention is specific for modified bases. and excises them to form abasic sites. However, the claims are interpreted in light of the specification, limitations from the specification are not read into the claims.

The response additionally argues that the probe DNA in the teachings of Chirikjian et al. is an exogenously added DNA, while in the present invention, the extended DNA is an endogenous DNA molecule, i.e. a piece of DNA produced in the reaction as part of the claimed process. Nevertheless, the teachings of Chirikjian et al. disclose that the 5' end of the probe upon cleavage has remained bound to the target polynucleotide can form a template for DNA polymerase (See column 8, lines 47-49).Thus, it is unclear whether the DNA used in the instant invention is exogenous or endogenous DNA. It appears that the DNA in claim 1 of the instant invention can be interpreted as an exogenous DNA or endogenous DNA.

Finally, regarding the argument of the reference of Dianov et al., the teachings of Dianov et al. encompass the limitations of claims 3-7 as set forth in the Office action mailed 7/05/2001.

Based upon the discussion above, the rejections are maintained. Each reaction is restates as follows.

2. claims 1-5, 8, 10-12, 14-16 and 20-21, 23 remain rejected under the judicially created doctrine of obviousness-type double patenting as being obvious over claims 1, 2, 4-7, 12-13 and 15-19 of McCarthy et al. U.S. Pat. No. 5,952,176 in view of Chirikjian et al. (5,656,430).

Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims 1-5, 8, 10-12, 14-16 and 20-23 are drawn to a method of characterizing nucleic acid molecules comprising introducing a modified base which is a substrate of DNA glycosylase into a DNA molecule, excising the modified based by the DNA glycosylase, cleaving the DNA at the abasic site to generate an upstream DNA fragment that can be extended in the presence of an enzyme and a template nucleic acid and analyzing the resultant fragments. The subject of the instant invention encompasses the method of claims 1, 2, 4-7, 12-13, 15-19 of U.S. Patent No. 5,952,176 because the claims are drawn to a method for rapidly detecting the presence or absence of a particular nucleic acid sequence at a candidate locus involving the steps in instant claims 1-5, 8, 10-12, 14-16 and 20-23 except that in the instant claims an upstream DNA fragment is formed by cleaving the DNA at the abasic site and extended. This technique is taught by Chirikjian et al.. Chirikjian et al. disclose a method for detecting point mutation in nucleic acid sequence in which 5' probe cleaved and binds to a template for DNA polymerase with dNTP (See column 8, lines 47-50).

3. Claims 1-2 and 8-21, 23 remain rejected under 35 U.S.C.§ 103(a) over McCarthy et al. (WO 97/03210) in view of Chirikjian et al. (5,656,430).

McCarthy et al. disclose a method for detecting a nucleic acid sequence at a locus in a target sample nucleic acid. The method involves introducing a modified base which is a substrate for a DNA glycosylase into a DNA molecule, excising the modified base by DNA glycosylase, cleaving phosphate linkages at abasic sites and analyzing the cleaved products of step iii) to identify the target nucleic acid (See pg. 8, lines 9-22) (as recited in claim 1-2, 4). The locus is amplified using normal DNA precursor nucleotides and at least one modified precursor nucleotide (See pg. 9, lines 5-6) (as recited in claims 10-12, 14, 15,16). The method is used for detecting multiple known mutation in DNA (See pg. 8, lines 23-27) (as recited in claim 21 and 23). The amplification method involves ligase chain reaction and deoxyribonucleotide (See pg. 9, lines 11-18) (as recited in claim 13, and 17). A modified nucleotide can be incorporated into a nucleic acid during amplification (See pg. 9, lines 18-20) (as recited in claim 8). One primer is labeled when an amplification method is used in the invention to allow detection of amplified target or complementary strand alone (See pg. 12, lines 7-10). The detection is done by using appropriate nucleic acid hybridization probe (See pg. 12, lines 22-25) (as recited in claim 20). This suggests that there must be a reporter oligonucleotide for the hybridization probe (as recited in 18). To facilitates detection of the cleaved extended adjacent primer, the extended adjacent primer denatured by denaturating polyacrylamide gel electrophoresis (See pg. 17, lines 9-18) (as recited in claim 9 that the amplified strands are separated for a separate analysis of the respective strands).

McCarthy et al. do not disclose that an upstream fragment formed as claimed is extended with a template and the extendible upstream fragment is incubated with ligase in the presence of a reporter oligonucleotide as recited in claim 18.

Chirikjian et al. disclose a method for detecting point mutation in nucleic acid sequence in which 5' probe cleaved and binds to a template for DNA polymerase with dNTP (See column 8, lines 47-50) and a probe is hybridized to single stranded DNA generating a mismatch in the ssDNA and the new strand is synthesized in vitro with DNA polymerase and ligase (See column 4, lines 7-12).

One of ordinary skill in the art at the time of instant invention would have been motivated to combine the teachings of McCarthy et al. and Chirikjian et al. to characterize nucleic acid molecules because the method of McCarthy et al. is used to detect multiple known mutations in DNA which can be achieved rapidly and easily (See pg. 8, lines 23-27) and the method of Chirikjian et al. is efficient and sensitive by using the probe (See column 8, lines 47-50) with labeled nucleotides for the signal (See column 2, lines 48 and column 8, lines 47-49). Thus, an ordinary skill in the art would have involved the probe as taught by Chirikjian et al. for characterizing nucleic acid. Thus, it would have been prima facie obvious to carry out the method as claimed.

4. Claims 3-7 remain rejected under 35 U.S.C.§ 103(a) over McCarthy et al. (WO 97/03210) in view of Chirikjian et al. (5,656,430) as applied to claims 1-2 and 8-23 above, and

further in view of Dianov et al. (Molecular and Cellular Biology, 1992, Vol. 12(4), pg. 1605-1612).

The teachings of McCarthy et al. and Chirikjian et al. are set forth in section 3 above and the methods of McCarthy et al. and Chirikjian et al. do not involving using 5' AP endonuclease and a 5' deoxyribophosphodiesterase as claimed in claims 3-7) to treat the apurinic and apyridimic sites (See pg. 23, lines 9-15).

Dianov et al. disclose that the extent and location of DNA repair synthesis in a double stranded oligonucleotide containing a single dUMP residue have been determined in which the repair pathway of a dUMP residue in DNA involves uracil- DNA glycosylase and incision of the phosphodiester bond 5' to AP site by an AP endonuclease and baseless sugar-phosphate residue could be excised by a dRpase or a 5'-3'exonuclease to leave a hydroxy group at the 3' terminus (See pg. 1606, fig, 1) (as recited in claims 3-6) and then the polymerase step occur either after of before the excision step. The excision step is catalyzed usually by a DNA deoxyribophosphodiesterase (See pg. 1605, the Abstract) (as recited in claim 7).

One of ordinary skill in the art at the time of instant invention would have been motivated to combine the teachings of McCarthy et al., Chirikjian et al. and Dianov et al. to characterize nucleic acid molecules because the method of McCarthy et al. is used to detect multiple known mutations in DNA which can be achieved rapidly and easily (See pg. 8, lines 23-27), the method of Chirikjian et al. is efficient and sensitive by using the probe (See column 8, lines 47-50) with labeled nucleotides for the signal (See column 2, lines 48 and column 8, lines 47-49), and the teachings of Dianov et al. indicate that the enzyme used in excision repair

involving AP sites is good candidates to carry out each step in the pathway (See pg. 16, column 1, last paragraph). Thus, it would have been prima facie obvious to carry out the method of characterizing DNA molecule with combining the teachings of McCarthy et al., Chirikjian et al. and Dianov et al.

Conclusion

5. Claims 1-21 and 23 are rejected for the reasons of record set forth above.

6. Any inquiries concerning this communication or earlier communications from the examiner should be directed to Joyce Tung whose telephone number is (703) 305-7112. The examiner can normally be reached on Monday-Friday from 8:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (703) 308-1119 on Monday-Friday from 10:00 AM-6:00 PM.

Any inquiries of a general nature or relating to the status of this application should be directed to the Chemical/Matrix receptionist whose telephone number is (703) 308-0196.

7. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Art Unit 1637 via the PTO Fax Center located in Crystal

Mall 1 using (703) 305-3014 or 308-4242. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Joyce Tung

May 7, 2003

Ethan Whisenant, Ph.D.
Primary Examiner
Art Unit 1634